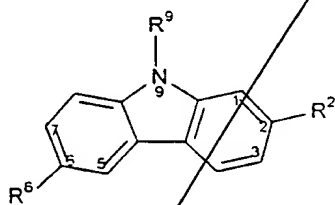


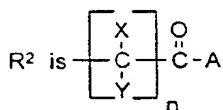
WHAT IS CLAIMED IS:

1. A method of treating or preventing pain and inflammatory processes and diseases associated with the activity of inducible cyclo-oxygenase-2 (COX-2) in a member of the species *Canis familiaris* in need of such treatment, while at the same time reducing or eliminating undesirable side effects associated with simultaneous inhibition of the activity of constitutive cyclo-oxygenase-1 (COX-1) by selectively inhibiting COX-2 activity with reference to COX-1 activity, wherein the selectivity ratio of COX-2 : COX-1 activity inhibition is at least 3 : 1 based on *ex vivo* inhibition levels in whole blood measured at a dose giving $\geq 80\%$ COX-2 inhibition, comprising administering to said member of the species *Canis familiaris* an amount therapeutically effective for treating pain and inflammation in accordance with the above-recited limitations, of an anti-inflammatory selective COX-2 inhibitory compound comprising a compound of the formula:



Formula (I)

20 wherein:



where A is hydroxy, (C₁ - C₄)alkoxy, amino, hydroxyamino, mono-(C₁ - C₂)alkylamino, di-(C₁ - C₂)alkylamino; X and Y are independently H or (C₁ - C₂)alkyl; and n is 1 or 2;

R⁶ is halogen, (C₁ - C₃)alkyl, trifluoromethyl, or nitro;

25 R⁹ is H; (C₁ - C₂)alkyl; phenyl or phenyl-(C₁ - C₂)alkyl, where phenyl is optionally mono-substituted by fluoro or chloro; -C(=O)-R, where R is (C₁ - C₂)alkyl or phenyl, optionally mono-substituted by fluoro or chloro; or -C(=O)-O-R¹, where R¹ is (C₁ - C₂)alkyl;

where X and Y are different, the (-)(R) and (+)(S) enantiomers thereof; and all

30 pharmaceutically acceptable salt forms, prodrugs and metabolites thereof which are therapeutically active for treating or preventing pain and inflammation.

71

5 2. A method of treating or preventing pain and inflammatory processes and diseases according to Claim 1 wherein said anti-inflammatory selective COX-2 inhibitory compound is carprofen, 6-chloro- α -methyl-9H-carbazole-2-acetic acid.

10 3. A method of treating or preventing pain and inflammatory processes and diseases according to Claim 1 wherein said anti-inflammatory selective COX-2 inhibitory compound is comprised entirely of (S)-enantiomer of carprofen, 6-chloro- α -methyl-9H-carbazole-2-acetic acid.

15 4. A method of treating or preventing inflammatory processes and diseases as in Claims 1, 2, or 3 further comprising wherein said inhibitory compound is used in combination with one or more other therapeutically active agents under the following conditions:

20 A. where a joint has become seriously inflamed as well as infected at the same time by bacteria, fungi, protozoa, and/or virus, said inhibitory compound is administered in combination with one or more antibiotic, antifungal, antiprotozoal, and/or antiviral therapeutic agents;

B. where a multi-fold treatment of pain and inflammation is desired, said inhibitory compound is administered in combination with inhibitors of other mediators of inflammation, comprising one or more members independently selected from the group consisting essentially of:

- 25 1. NSAIDs;
2. H₁-receptor antagonists;
3. kinin-B₁- and B₂-receptor antagonists;
4. prostaglandin inhibitors selected from the group consisting of PGD-, PGF-PGI₂-, and PGE-receptor antagonists;
- 30 5. thromboxane A₂ (TXA₂-) inhibitors;
6. 5- and 12-lipoxygenase inhibitors;
7. leukotriene LTC₄-, LTD₄/LTE₄-, and LTB₄-inhibitors;
8. PAF-receptor antagonists;
9. gold in the form of an aurothio group together with one or more hydrophilic
- 35 groups;
10. immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine, and methotrexate;
11. anti-inflammatory glucocorticoids;

5

12. penicillamine;

13. hydroxychloroquine;

14. anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfinpyrazone, and benzbromarone;

10

C. where older dogs are being treated for disease conditions, syndromes and symptoms found in geriatric dogs, said inhibitory compound is administered in combination with one or more members independently selected from the group consisting essentially of:

1. cognitive therapeutics to counteract memory loss and impairment;

2. anti-hypertensives and other cardiovascular drugs intended to offset the

15

consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure, and myocardial infarction, selected from the group consisting of:

a. diuretics;

b. vasodilators;

c. β -adrenergic receptor antagonists;

20

d. angiotensin-II converting enzyme inhibitors (ACE-inhibitors), alone or optionally together with neutral endopeptidase inhibitors;

e. angiotensin II receptor antagonists;

f. renin inhibitors;

g. calcium channel blockers;

25

h. sympatholytic agents;

i. α_2 -adrenergic agonists;j. α -adrenergic receptor antagonists; and

k. HMG-CoA-reductase inhibitors (anti-hypercholesterolemics);

3. antineoplastic agents selected from:

30

a. antimitotic drugs selected from:

i. vinca alkaloids selected from:

[1] vinblastine, and

[2] vincristine;

4. growth hormone secretagogues;

35

5. strong analgesics;

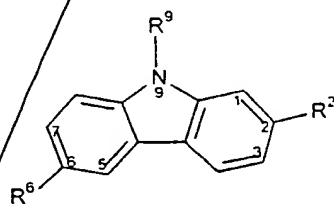
6. local and systemic anesthetics; and

7. H_2 -receptor antagonists, proton pump inhibitors, and other gastroprotective

agents.

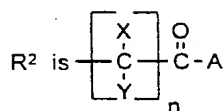
5 Sub C3
5. A pharmaceutical composition for treating or preventing pain and inflammatory processes and diseases associated with the activity of inducible cyclo-oxygenase-2 (COX-2) in a member of the species *Canis familiaris* in need of such treatment, while at the same time reducing or eliminating undesirable side effects associated with simultaneous inhibition of the
10 activity of constitutive cyclo-oxygenase-1 (COX-1), comprising:

A. a therapeutically effective amount for treating pain and inflammation, of an anti-inflammatory selective COX-2 inhibitory compound which selectively inhibits COX-2 activity with reference to COX-1 activity, wherein the selectivity ratio of COX-2 : COX-1 activity inhibition is at least 3 : 1 based on *ex vivo* inhibition levels in whole blood measured at a dose
15 giving $\geq 80\%$ COX-2 inhibition, comprising an anti-inflammatory selective COX-2 inhibitory compound comprising a compound of the formula:



Formula (I):

20 wherein:



where A is hydroxy, (C₁ - C₄)alkoxy, amino, hydroxyamino, mono-(C₁ - C₂)alkylamino, di-(C₁ - C₂)alkylamino; X and Y are independently H or (C₁ - C₂)alkyl; and n is 1 or 2;

R⁶ is halogen, (C₁ - C₃)alkyl, trifluoromethyl, or nitro;

25 R⁹ is H; (C₁ - C₂)alkyl; phenyl or phenyl-(C₁ - C₂)alkyl, where phenyl is optionally mono-substituted by fluoro or chloro; -C(=O)-R, where R is (C₁ - C₂)alkyl or phenyl, optionally mono-substituted by fluoro or chloro; or -C(=O)-O-R¹, where R¹ is (C₁ - C₂)alkyl;

where X and Y are different, the (-)(R) and (+)(S) enantiomers thereof; and all
30 pharmaceutically acceptable salt forms, prodrugs and metabolites thereof which are therapeutically active for treating or preventing pain and inflammation; and

Sub
5C3
cont.

B. a pharmaceutically acceptable carrier therefor.

6. A pharmaceutical composition according to Claim 5 wherein said anti-inflammatory selective COX-2 inhibitory compound is carprofen, 6-chloro- α -methyl-9H-carbazole-2-acetic acid.

10 7. A pharmaceutical composition according to Claim 5 wherein said anti-inflammatory selective COX-2 inhibitory compound is comprised entirely of (S)-enantiomer of carprofen, 6-chloro- α -methyl-9H-carbazole-2-acetic acid.

Sub
5C4

15 8. A pharmaceutical composition as in Claims 5, 6, or 7 further comprising wherein said anti-inflammatory selective COX-2 inhibitory compound is provided in a dosage form suitable for systemic administration by:

20 A. injection or infusion in suitable liquid form which is intraarterial, intra- or transdermal, subcutaneous, intramuscular, intraspinal, intrathecal, or intravenous, wherein said inhibitory compound:

1. is contained in solution as a solute;

2. is contained in the discontinuous phase of an emulsion, or the discontinuous phase of an inverse emulsion which inverts upon injection or infusion, said emulsions containing suitable emulsifying agents; or

25 3. is contained in a suspension as a suspended solid in colloidal or microparticulate form, said suspension containing suitable suspending agents;

B. injection or infusion into suitable body tissues or cavities as a depot, wherein said composition provides storage of said inhibitor and thereafter delayed-, sustained-, and/or controlled-release of said inhibitory compound for systemic distribution;

30 C. instillation, inhalation or insufflation into suitable body tissues or cavities in suitable solid form, where said inhibitory compound:

1. is contained in a solid implant composition providing delayed-, sustained-, and/or controlled-release of said inhibitory compound;

2. is contained in a particulate composition to be inhaled into the lungs; or

35 3. is contained in a particulate composition to be blown into said suitable body tissues or cavities, wherein said composition optionally provides delayed-, sustained-, and/or controlled-release of said inhibitory compound; or

5

D. ingestion in suitable solid or liquid form for peroral delivery of said inhibitory compound, where said inhibitory compound:

1. is contained in a solid dosage form; or
2. is contained in a liquid dosage form.

10

9. A pharmaceutical composition according to Claim 8 wherein said dosage forms comprise one or more members selected independently from the group consisting essentially of suppositories; solid peroral dosage forms selected from the group consisting of delayed-release tablets, capsules, caplets, lozenges, troches, and multiparticulates; enteric-coated tablets and capsules which prevent release and absorption in the stomach of said member

15

being treated to facilitate delivery distal to the stomach of said member; sustained-release oral tablets, capsules and microparticulates which provide systemic delivery of said inhibitor in a controlled manner over at least a 10-hour period; a chewable or ingestible oral tablet; a unit dose packet sachet, a suspension made from said unit dose packet sachet, a powder for oral suspension, or an oral suspension *per se*; a fast-dissolving tablet; encapsulated solutions; an

20

oral paste; a granular form incorporated in or to be incorporated in said member's food; and a palatable chewable form in which said inhibitor is consumed along with said palatable chewable form, or is delivered by leaching from said chew, which is not consumed, during mastication by said member being treated; liquid peroral dosage forms selected from the group consisting of solutions, suspensions, emulsions, inverse emulsions, elixirs, extracts,

25

tinctures, and concentrates; and the above-recited solid dosage forms containing microencapsulated formulations of the active ingredient, which is incorporated into said solid dosage form.

30

10. A pharmaceutical composition as in Claim 9 comprising an oral controlled release carprofen dosage form able to maintain plasma carprofen levels above approximately 10 µg/mL for a period of time greater than 10.5 hours, when administered at a dose of about 2 mg/lb or less.

35

11. A pharmaceutical composition as in Claims 5, 6, or 7 further comprising said anti-inflammatory selective COX-2 inhibitory compound in combination with one or more other therapeutically active agents independently selected from the group consisting essentially of:

A. anti-infectious agents comprising one or more antibiotic, antifungal, antiprotozoal, or antiviral therapeutic agents;

Sub
B3⁵
cont

B. inhibitors of other mediators of inflammation, comprising one or more members independently selected from the group consisting essentially of:

1. NSAIDs;
2. H₁-receptor antagonists;
3. kinin-B₁- and B₂-receptor antagonists;
- 10 4. prostaglandin inhibitors selected from the group consisting of PGD-, PGF-PGI₂ -, and PGE-receptor antagonists;
5. thromboxane A₂ (TXA₂-) inhibitors;
6. 5- and 12-lipoxygenase inhibitors;
7. leukotriene LTC₄ -, LTD₄/LTE₄ -, and LTB₄ -inhibitors;
- 15 8. PAF-receptor antagonists;
9. gold in the form of an aurothio group together with one or more hydrophilic groups;
10. immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine, and methotrexate;
- 20 11. anti-inflammatory glucocorticoids;
12. penicillamine;
13. hydroxychloroquine;
14. anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfinpyrazone, and benzbromarone;
- 25

C. therapeutic agents for the treatment of geriatric dogs comprising one or more members independently selected from the group consisting essentially of:

1. cognitive therapeutics to counteract memory loss and impairment;
2. anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure, and myocardial infarction, selected from the group consisting of:
 - a. diuretics;
 - b. vasodilators;
 - c. β -adrenergic receptor antagonists;
 - 35 d. angiotensin-II converting enzyme inhibitors (ACE-inhibitors), alone or optionally together with neutral endopeptidase inhibitors;
 - e. angiotensin II receptor antagonists;
 - f. renin inhibitors;

Sub⁵
P3
Cont

10

- g. calcium channel blockers;
- h. sympatholytic agents;
- i. α_2 -adrenergic agonists;
- j. α -adrenergic receptor antagonists; and
- k. HMG-CoA-reductase inhibitors (anti-hypercholesterolemics);

3. antineoplastic agents selected from:

- a. antimitotic drugs selected from:

- i. vinca alkaloids selected from:

- [1] vinblastine, and

- [2] vincristine;

15

4. growth hormone secretagogues;

5. strong analgesics;

6. local and systemic anesthetics; and

7. H_2 -receptor antagonists, proton pump inhibitors, and other gastroprotective

agents.

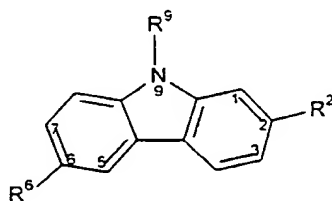
20

12. A package suitable for use in commerce for the therapeutic treatment or prevention of pain and inflammation processes and diseases in a member of the species *Canis familiaris* in need of such treatment, comprising:

25

A. a suitable container optionally in the form of an outer package and an inner container removably housed therein;

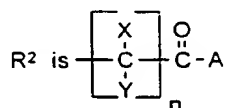
B. a suitable dosage form, enclosed in said container, of an anti-inflammatory selective COX-2 inhibitory compound of the formula:



Formula (I):

30

wherein:



5 where A is hydroxy, (C₁ - C₄)alkoxy, amino, hydroxyamino, mono-(C₁ - C₂)alkylamino, di-(C₁ - C₂)alkylamino; one of X and Y is H and the other is (C₁ - C₂)alkyl; and n is 1 or 2;

R⁶ is halogen, (C₁ - C₃)alkyl, trifluoromethyl, or nitro;

10 R⁹ is H; (C₁ - C₂)alkyl; phenyl or phenyl-(C₁ - C₂)alkyl, where phenyl is optionally mono-substituted by fluoro or chloro; -C(=O)-R, where R is (C₁ - C₂)alkyl or phenyl, optionally mono-substituted by fluoro or chloro; or -C(=O)-O-R¹, where R¹ is (C₁ - C₂)alkyl;

wherein (+)(S) enantiomer is present in amount of at least 75%; and all pharmaceutically acceptable salt forms, prodrugs and metabolites thereof which are therapeutically active for treating or preventing pain and inflammation; and

15 C. printed instructional and informational material associated with said container, which is attached to said container, enclosed in said container, or displayed as an integral part of said container, said instructional and informational material stating in words which convey to a reader thereof of ordinary skill in the art that said compound of Formula (I) comprising a therapeutic agent contained in said package, when administered to said member of the species *Canis familiaris* to be treated, effectively inhibits cyclo-oxygenase-2 (COX-2) induced at an existing or expected site of pain and inflammation in said dog, thereby treating or preventing said pain and inflammation which would otherwise result therefrom, while at the same time reducing or eliminating undesirable side effects associated with simultaneous inhibition of the activity of constitutive cyclo-oxygenase-1 (COX-1) by selectively inhibiting
20 COX-2 activity with reference to COX-1 activity, wherein the selectivity ratio of COX-2 : COX-1 activity inhibition is at least 3 : 1 based on *ex vivo* inhibition levels in whole blood measured at a dose giving $\geq 80\%$ COX-2 inhibition.

30 13. A package according to Claim 12 wherein said anti-inflammatory selective COX-2 inhibitory compound of Formula (I) comprises carprofen, 6-chloro- α -methyl-9H-carbazole-2-acetic acid.

35 14. A package according to Claim 12 wherein said anti-inflammatory selective COX-2 inhibitory compound is comprised entirely of (S)-enantiomer of carprofen, 6-chloro- α -methyl-9H-carbazole-2-acetic acid.